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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,580	MOCIKAT, RALPH	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 25-30* is/are pending in the application.

4a) Of the above claim(s) *25-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/064026.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/18/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-17) in the reply filed on 11 December 2006 is acknowledged. The traversal is on the ground(s) that the vector of Group I is closely related to the method of using the vector, comprising Group II (claims 25-30). This is not found persuasive because Groups I and II are related as product and process of use. As stated in the Requirement for Restriction/Election mailed on 10 October 2006, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the method of Group II could be practiced with an immunoglobulin-cytokine fusion protein. Additionally, Group I could be used *in vitro* for the production of an immunoglobulin-cytokine fusion protein or could be used for expression in bacteria. These inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification. As such, restriction for examination purposes as indicated is proper.

As stated in the Requirement for Restriction/Election mailed on 10 October 2006, the Examiner has required restriction between product and process claims. Where Applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be

amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01. At the present time, none of the product claims are allowable.

The previous Examiner also required several species elections. In the interest of advancing prosecution, the species elections are withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-17 and 25-30 are pending. Claims 18-24 have been cancelled by Applicant. Claims 25-30 are withdrawn as being directed to a non-elected invention. Claims 1-17 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 18 November 2003 has been being considered by the examiner to the fullest extent possible. The German Patent Application DE 4406512C1 was not considered because the entire document is published in German and no English equivalency was provided or could be found. A copy of the German language version of DE 4406512C1 is present in the parent US application 09/064,026. The DE 4406512C12 will be considered by the Examiner if a translation or an English language equivalent is provided. The German Patent Application DE 19541405A1 was considered insofar as an English translation was available as US Patent 6,521,449 (18 February 2003), claiming priority to DE 19541450 (7 November 1995). A copy of the German language version of DE 19541405A1 is present in the parent US Application 09/064,026. A signed copy of the IDS is attached hereto.

Claim Objections

4. Claims 1-17 are objected to because of the following informalities: there are no articles such as "a" or "the" preceding the word "vector" in the claims. It is suggested that claim 1 should recite the phrase "A vector..." and all dependent claims should recite the phrase "The vector of claim 1..." Additionally, there appears to be a typographical error in claim 1 (d). The claim recites "a market gene..." In order to expedite prosecution, the Examiner will interpret this phrase to recite "a marker gene..."Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) cloned into pSVgpt-huγ1-A5, does not reasonably provide enablement for a genera of vectors encoding generic cytokine-immunoglobulin fusion proteins; a genera of vectors encoding a genera of immunoglobulins; a genera of vectors comprising DNA encoding a cytokine; a genera of vectors encoding a genera of marker genes; a genera of vectors encoding a genera of enhancers; a genera of vectors encoding a genera of nucleic acids homologous to a region comprising the Cμ or Cκ enhancer; a genera of vectors encoding a genera of bacterially compatible regulatory units; a genera of vectors encoding a genera of domains from a human immunoglobulin chain; a genera of vectors encoding a genera of non-species specific chimeric immunoglobulins; a genera of vectors encoding a genera of interleukins; a genera of vectors encoding a genera of interferons; a genera of vectors encoding a genera of colony-stimulating factors; a genera of vectors encoding a genera of lymphokines; or a genera of vectors encoding a genera of growth factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite [a] vector for the expression of immunoglobulin-cytokine fusion proteins in malignant B cells comprising the following components operably linked to each other (a) a region of at least 1.5 kb which is homologous to a region of the μ intron or the κ intron, (b) at least one DNA sequence encoding a domain of an immunoglobulin or a functional part thereof,(c) a DNA sequence encoding a cytokine, and (d) a marker gene which is selectable in

eukaryotic B cells and contains a functional enhancer region; [the] vector according to claim 1, wherein said region of at least 1.5 kb contains a functional Cμ or Cκ enhancer; wherein said region of at least 1.5 kb contains a non-functional Cμ or Cκ enhancer; wherein the marker gene selectable in eukaryotic B cells contains a non-functional enhancer region; wherein the marker gene selectable in eukaryotic B cells lacks an enhancer region; wherein the DNA sequence of (b) encodes a constant region or a part thereof; wherein the region homologous to a region comprising the Cμ or the Cκ enhancer of the μ or the κ intron comprises at least 1.9 kb; wherein the region homologous to a region comprising the Cμ or Cκ enhancer of the μ or the κ intron comprises at least 2.0 kb; said vector containing a regulatory unit which is compatible with bacteria; wherein the immunoglobulin is a chimeric immunoglobulin; wherein the DNA sequence of (b) encodes the domain of a human immunoglobulin chain; wherein the DNA sequence of (b) encodes domains derived from mouse, rat, goat, horse or sheep; wherein the DNA sequence of (b) encodes all the C domains of a secretory antibody; wherein the DNA sequence according to (b) encodes all the C domains of a membrane-bound antibody; characterized in that said DNA sequence of (c) encodes interleukins, interferons, colony-stimulating factors, lymphokins or growth factors; characterized in that said DNA sequence of (c) encodes IL-2, IL-4, IL-7, IL-12, IL-13, GM-CSF or interferon γ; wherein the selectable marker gene is gpt, neo or a marker gene encoding hygromycin resistance.

The nature of the invention is drawn to a genus of vectors encoding immunoglobulin-cytokine fusion proteins. The state of the art discloses that B cell lymphoma tumor-associated antigens coupled to immune response-enhancing cytokines, such as GM-CSF, IL-2 and IL-4, to produce an immune response to the tumor antigen and enhance the ability of the host to resist tumor growth associated with the antigen, are well known in the art (see Levy et al., US Patent 6,099,846 (8 August 2000); Polack et al., US Patent 6,521,499 (18 February 2003); and Gilles et al., US Patent 5,650,150 (22 July 1997)). It is also well known that the immunogenicity of antigens can be enhanced by coupling these hapten-bearing moieties to carriers. A variety of carriers are routinely used, such as keyhole limpet hemocyanin, various serum albumins, and cytokines ('846 patent, column 1, lines 31-34). It is also understood that certain cytokines, such as GM-CSF, have the capacity to enhance primary antibody responses to antigens ('846 patent, column 1, lines 34-38).

The level of skill of those in the art is high, but generating vectors comprising fusion proteins was old, common place, and well known in the art at the time the instant invention was made. There is one working model of a recombinant immunoglobulin-cytokine fusion protein

disclosed in the specification. A vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) was cloned into pSVgpt-huγ1-A5 (pp. 13-14 of the specification – labeled pages 17 and 18). The pSP72 vector is a commercially available vector (see instant Figure 3). The pSVgpt-huγ1-A5 construct used was well known in the art (see specification pp. 13 (labeled 17), last sentence, to p. 14 (labeled 18), first sentence).

Applicants' claims are excessively broad due. Applicant's claims are drawn to a genera of vectors encoding generic cytokine-immunoglobulin fusion proteins, a genera of vectors encoding a genera of immunoglobulins, a genera of vectors comprising DNA encoding a cytokine, a genera of vectors encoding a genera of marker genes, a genera of vectors encoding a genera of enhancers, a genera of vectors encoding a genera of nucleic acids homologous to a region comprising the Cμ or Cκ enhancer, a genera of vectors encoding a genera of bacterially compatible regulatory units, a genera of vectors encoding a genera of domains from a human immunoglobulin chain, a genera of vectors encoding a genera of non-species specific chimeric immunoglobulins, a genera of vectors encoding a genera of interleukins, a genera of vectors encoding a genera of interferons, a genera of vectors encoding a genera of colony-stimulating factors, a genera of vectors encoding a genera of lymphokines, and a genera of vectors encoding a genera of growth factors. It would be undue experimentation to make even a small number of permutations from all of the possible combinations of components that Applicant claims to construct the recited genera of vectors. Applicant has provided only one working example of one such vector (see specification pp. 13-14; labeled pp. 17-18). Although working examples and data are not required, they do provide guidance that shows how to make or use the claimed invention. Additionally, the art teaches other vectors comprising IgG-Fc-GM-CSF, IgG-Fc-IL-2, and IgG-Fc-IL-4, for example. However, neither the art nor the instant specification teach the range of claimed vectors encoding cytokine-immunoglobulin fusion proteins. Applicant has failed to provide structural or functional guidance to support the breadth and scope of the claims, as written. Structure is critical to making and using vectors because they are composed of nucleic acids in a certain structural order. One of ordinary skill in the art cannot begin to make a vector without knowing the sequence of "a region of 1.5kb which is homologous to a region of the μ intron or the κ intron. One of ordinary skill in the art cannot begin to make a vector for the expression of an immunoglobulin-cytokine fusion protein without some guidance on selecting the cytokine to be encoded or the type and region of the immunoglobulin domain to be used. One of ordinary skill in the art would not be able to discern which enhancer is used in Applicant's invention because the claims and the specification do not recite the structure of a sufficient

number of enhancers such that one of skill in the art would be apprised of the claimed genus of enhancers that could be used. Construction of such vectors would be entirely unpredictable without additional guidance. It is likely that one of skill in the art would have to construct tens of thousands of vectors and test the same for functionality before it could be determined which vectors fall within the scope of Applicant's claims. Moreover, without knowing the sequence structure of such vectors, one would not be able to predict their function.

Applicant admits in the specification that methods of carrying out transfection or retroviral gene transfer are old and well known in the art (see p. 10 – labeled as page 15, second paragraph). Applicant also acknowledges that transfection of immunoglobulin-producing cells is also regarded as standard procedure in modern immunology (p. 9, labeled as p. 14, last paragraph).

Applicant claims a vector according to claim 1 wherein the DNA sequence of part (b), which encodes a domain of an immunoglobulin or a functional part thereof, is derived from mouse, rat, goat, horse, or sheep. Applicant has not provided sufficient guidance in the specification such that one of skill in the art could determine which functional parts of which types of immunoglobulins from rats, goats, horses, or sheep, are to be used in the claimed genus of vectors. No structure or function of the "functional part" of the immunoglobulins are taught in the specification.

A non-functional enhancer is not defined in the specification. Applying the ordinary meaning to the phrase "non-functional enhancer," one of skill in the art would presume that expression of some portion of the encoded fusion protein would be abolished by using a non-functional enhancer. As such, it is unclear whether Applicant intends the nucleic acid sequence homologous to the Cμ or Cκ introns to be silenced or whether the expression of some other portion of the claimed vector is to be abolished by the inclusion of a non-functional enhancer. There is no guidance in the specification as to what non-functional enhancer is to be used or what mutations, deletions, or substitutions can be made in functional enhancers to render them non-functional. It is unclear whether the term "non-functional enhancer" merely refers to an intron coding region rather than a "functional" exon coding region or whether something else is intended by the term "non-functional." As such, one would not know how to make or use the recited vector comprising a non-functional enchancer region without undue experimentation.

The claims recite a vector for the expression of immunoglobulin-cytokine fusion proteins comprising "a functional part" of an immunoglobulin. There is no guidance in the specification as to which parts of an immunoglobulin would be considered functional for purposes of creating

the claimed genus of vectors. No structural guidance is provided and there is no guidance as to the function of the "functional part" such that a region of an immunoglobulin could be determined by a known function.

The claims recite "a functional part of a constant region" in claim 6, for example. It is unclear whether this term refers to an Fc region, a CH1, CH2, or CH3 region and from which antibody type (i.e. IgG) and subtype (i.e. IgG1, IgG2, IgG3, or IgG4) in which species? There is no guidance in the specification to determine which structural or functional region of a constant region of an immunoglobulin is meant. As such, it would require undue experimentation to make and/or use the invention, as claimed.

It is also unclear which regulatory elements Applicant means when "bacterially compatible regulatory units" are recited in the claims. It would require undue experimentation to determine all of the potential bacterially compatible regulatory units that could be used and test the same for functionality.

The claims also recite that the "DNA sequence of [claim 1 subpart] (c) encodes interleukins, interferons, colony-stimulating factors, lymphokines, or growth factors. Applicant has not provided guidance in the specification for the genus of DNA encoding the recited generas of interleukins, interferons, colony-stimulating factors, lymphokines, or growth factors. As such, it would be undue experimentation to determine the applicable structural DNA sequence for every interleukin, interferon, colony-stimulating factor, lymphokine, and growth factor, in any species, incorporate it into the recited vector, and test the same for functionality.

Due to the large quantity of experimentation necessary to determine the sequence structure and function of the multiple generas of component parts needed to construct the tens of thousands of potential vectors claimed, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that knowing the structure of a vector is critical to its functionality, and the breadth of the claims which fail to recite specific DNA coding sequences, specific cytokine-immunoglobulin fusion proteins, specific sequences homologous to a region comprising the Cμ or Cκ enhancer, specific bacterially compatible regulatory units, specific constant domains from a human immunoglobulin chain, and specific chimeric immunoglobulins from any combination of species, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

7. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite [a] vector for the expression of immunoglobulin-cytokine fusion proteins in malignant B cells comprising the following components operably linked to each other (a) a region of at least 1.5 kb which is homologous to a region of the μ intron or the κ intron, (b) at least one DNA sequence encoding a domain of an immunoglobulin or a functional part thereof,(c) a DNA sequence encoding a cytokine, and (d) a marker gene which is selectable in eukaryotic B cells and contains a functional enhancer region; [the] vector according to claim 1, wherein said region of at least 1.5 kb contains a functional Cμ or Cκ enhancer; wherein said region of at least 1.5 kb contains a non-functional Cμ or Cκ enhancer; wherein the marker gene selectable in eukaryotic B cells contains a non-functional enhancer region; wherein the marker gene selectable in eukaryotic B cells lacks an enhancer region; wherein the DNA sequence of (b) encodes a constant region or a part thereof; wherein the region homologous to a region comprising the Cμ or the Cκ enhancer of the μ or the κ intron comprises at least 1.9 kb; wherein the region homologous to a region comprising the Cμ or Cκ enhancer of the μ or the κ intron comprises at least 2.0 kb; said vector containing a regulatory unit which is compatible with bacteria; wherein the immunoglobulin is a chimeric immunoglobulin; wherein the DNA sequence of (b) encodes the domain of a human immunoglobulin chain; wherein the DNA sequence of (b) encodes domains derived from mouse, rat, goat, horse or sheep; wherein the DNA sequence of (b) encodes all the C domains of a secretory antibody; wherein the DNA sequence according to (b) encodes all the C domains of a membrane-bound antibody; characterized in that said DNA sequence of (c) encodes interleukins, interferons, colony-stimulating factors, lymphokins or growth factors; characterized in that said DNA sequence of (c) encodes IL-2, IL-4, IL-7, IL-12, IL-13, GM-CSF or interferon γ; wherein the selectable marker gene is gpt, neo or a marker gene encoding hygromycin resistance.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a genera of vectors encoding generic cytokine-immunoglobulin fusion proteins; a genera of vectors encoding a genera of immunoglobulins; a genera of vectors comprising DNA encoding a cytokine; a genera of vectors encoding a genera of marker genes; a genera of vectors encoding a genera of enhancers; a genera of vectors encoding a genera of nucleic acids homologous to a region comprising the Cμ or Cκ enhancer; a genera of vectors encoding a genera of bacterially compatible regulatory units; a genera of vectors encoding a genera of domains from a human immunoglobulin chain; a genera of vectors encoding a genera of non-species specific chimeric immunoglobulins; a genera of vectors encoding a genera of interleukins; a genera of vectors encoding a genera of interferons; a genera of vectors encoding a genera of colony-stimulating factors; a genera of vectors encoding a genera of lymphokines; or a genera of vectors encoding a genera of growth factors.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* a vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) cloned into pSVgpt-huγ1-A5 (pp. 13-14 of the specification – labeled pages 17 and 18). The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a genera of vectors encoding generic cytokine-immunoglobulin fusion proteins; a genera of vectors encoding a genera of immunoglobulins; a genera of vectors comprising DNA encoding a cytokine; a genera of vectors encoding a genera of marker genes; a genera of vectors encoding a genera of enhancers; a genera of vectors encoding a genera of nucleic acids homologous to a region comprising the Cμ or Cκ enhancer; a genera of vectors encoding a genera of bacterially compatible regulatory units; a genera of vectors encoding a genera of domains from a human immunoglobulin chain; a genera of vectors encoding a genera of non-species specific chimeric immunoglobulins; a genera of vectors encoding a genera of interleukins; a genera of vectors encoding a genera of interferons; a genera of vectors encoding a genera of colony-stimulating factors; a genera of vectors encoding a genera of lymphokines; or a genera of vectors encoding a genera of growth factors. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the claimed generas. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a vector comprising a region of at least 1.5kb which is homologous to a region of the μ or the κ intron. Claim 7 recites a region homologous to a region comprising the Cμ or the Cκ enhancer of the μ or the κ intron comprises at least 1.9 kb. Claim 8 recites a

region homologous to a region comprising the Cμ or Cκ enhancer of the μ or the κ intron comprises at least 2.0 kb. There is no upper limit to the size of the genus of homologous nucleic acid kilobases claimed. The lower limit of 1.5kb, 1.9kb, and 2.0kb are recited, but because there is no upper limited to any of the claimed homologous regions, the metes and bounds of the claim are not limited.

10. Claims 1 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 recites that the DNA sequence "encodes domains derived from mouse, rat, goat, horse, or sheep." However, the term "derived" is unclear and confusing.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-9, 11, and 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. It is noted that the instant inventor Mocikat is not listed as an inventor on the '449 patent.

The claims recite [a] vector for the expression of immunoglobulin-cytokine fusion proteins in malignant B cells comprising the following components operably linked to each other (a) a region of at least 1.5 kb which is homologous to a region of the μ intron or the κ intron, (b) at least one DNA sequence encoding a domain of an immunoglobulin or a functional part thereof,(c) a DNA sequence encoding a cytokine, and (d) a marker gene which is selectable in

eukaryotic B cells and contains a functional enhancer region; [the] vector according to claim 1, wherein said region of at least 1.5 kb contains a functional Cμ or Cκ enhancer; wherein said region of at least 1.5 kb contains a non-functional Cμ or Cκ enhancer; wherein the marker gene selectable in eukaryotic B cells contains a non-functional enhancer region; wherein the marker gene selectable in eukaryotic B cells lacks an enhancer region; wherein the DNA sequence of (b) encodes a constant region or a part thereof; wherein the region homologous to a region comprising the Cμ or the Cκ enhancer of the μ or the κ intron comprises at least 1.9 kb; wherein the region homologous to a region comprising the Cμ or Cκ enhancer of the μ or the κ intron comprises at least 2.0 kb; said vector containing a regulatory unit which is compatible with bacteria; wherein the immunoglobulin is a chimeric immunoglobulin; wherein the DNA sequence of (b) encodes the domain of a human immunoglobulin chain; wherein the DNA sequence of (b) encodes domains derived from mouse, rat, goat, horse or sheep; wherein the DNA sequence of (b) encodes all the C domains of a secretory antibody; wherein the DNA sequence according to (b) encodes all the C domains of a membrane-bound antibody; characterized in that said DNA sequence of (c) encodes interleukins, interferons, colony-stimulating factors, lymphokins or growth factors; characterized in that said DNA sequence of (c) encodes IL-2, IL-4, IL-7, IL-12, IL-13, GM-CSF or interferon γ; wherein the selectable marker gene is gpt, neo or a marker gene encoding hygromycin resistance.

The '449 patent teaches gene constructs of cytokine-immunoglobulin fusion proteins in malignant B-cells comprising enhancers from the immunoglobulin μ and κ locus, the immunoglobulin heavy chain μ locus, and the immunoglobulin λ locus, a promoter and polyadenylation site (see abstract, Figure 1; column 4, lines 30-67 to column 5, lines 1-58; and column 8, lines 1-30). μ and κ locus intron [i.e. non-functional] enhancers are taught at column 4, lines 37-54. Immunoglobulin heavy chain μ locus is taught at column 4, line 54. An immunoglobulin κE3' region is taught at column 8, lines 29-30. κ locus exon enhancers [i.e. functional enhancers] are taught at column 4, line 38. Coding regions of 2.6kb are taught at column 8, line 5. Sequences encoding cytokine genes of interest are taught at column 4, lines 56-57. Specific cytokine genes for IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, GM-CSF, G-CSF, TNFα, MCP-1, and IFNγ are taught at column 5, lines 55-58, column 7, lines 45-47, column 8, lines 59-63, and column 9, line 64. Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are taught at column 4, lines 59-60, and column 5, lines 21-26, including hygromycin resistance gene and a neomycin resistance gene. Vectors preferably containing sequences derived from bacterial vectors are taught at column 5, lines 15-16. A vector

construct lacking the enhancer cassette and marker are taught at column 9, lines 2-4. Human immunoglobulin κ locus is taught at column 3, line 52.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-13, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996) in view of Levy et al., US Patent 6,009,846 (8 August 2000, benefit to 14 April 1995) and Gillies et al., US Patent 5,650,150 (22 July 1997, benefit to 7 November 1991).

The claims recite [a] vector for the expression of immunoglobulin-cytokine fusion proteins in malignant B cells comprising the following components operably linked to each other (a) a region of at least 1.5 kb which is homologous to a region of the μ intron or the κ intron, (b) at least one DNA sequence encoding a domain of an immunoglobulin or a functional part thereof,(c) a DNA sequence encoding a cytokine, and (d) a marker gene which is selectable in

eukaryotic B cells and contains a functional enhancer region; [the] vector according to claim 1, wherein said region of at least 1.5 kb contains a functional Cμ or Cκ enhancer; wherein said region of at least 1.5 kb contains a non-functional Cμ or Cκ enhancer; wherein the marker gene selectable in eukaryotic B cells contains a non-functional enhancer region; wherein the marker gene selectable in eukaryotic B cells lacks an enhancer region; wherein the DNA sequence of (b) encodes a constant region or a part thereof; wherein the region homologous to a region comprising the Cμ or the Cκ enhancer of the μ or the κ intron comprises at least 1.9 kb; wherein the region homologous to a region comprising the Cμ or Cκ enhancer of the μ or the κ intron comprises at least 2.0 kb; said vector containing a regulatory unit which is compatible with bacteria; wherein the immunoglobulin is a chimeric immunoglobulin; wherein the DNA sequence of (b) encodes the domain of a human immunoglobulin chain; wherein the DNA sequence of (b) encodes domains derived from mouse, rat, goat, horse or sheep; wherein the DNA sequence of (b) encodes all the C domains of a secretory antibody; wherein the DNA sequence according to (b) encodes all the C domains of a membrane-bound antibody; characterized in that said DNA sequence of (c) encodes interleukins, interferons, colony-stimulating factors, lymphokins or growth factors; characterized in that said DNA sequence of (c) encodes IL-2, IL-4, IL-7, IL-12, IL-13, GM-CSF or interferon γ; wherein the selectable marker gene is gpt, neo or a marker gene encoding hygromycin resistance.

The '449 patent teaches gene constructs of cytokine-immunoglobulin fusion proteins in malignant B-cells comprising enhancers from the immunoglobulin μ and κ locus, the immunoglobulin heavy chain μ locus, and the immunoglobulin λ locus, a promoter and polyadenylation site (see abstract, Figure 1; column 4, lines 30-67 to column 5, lines 1-58; and column 8, lines 1-30). μ and κ locus intron [i.e. non-functional] enhancers are taught at column 4, lines 37-54. Immunoglobulin heavy chain μ locus is taught at column 4, line 54. An immunoglobulin κE3' region is taught at column 8, lines 29-30. κ locus exon enhancers [i.e. functional enhancers] are taught at column 4, line 38. Coding regions of 2.6kb are taught at column 8, line 5. Sequences encoding cytokine genes of interest are taught at column 4, lines 56-57. Specific cytokine genes for IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, GM-CSF, G-CSF, TNFα, MCP-1, and IFNγ are taught at column 5, lines 55-58, column 7, lines 45-47, column 8, lines 59-63, and column 9, line 64. Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are taught at column 4, lines 59-60, and column 5, lines 21-26, including hygromycin resistance gene and a neomycin resistance gene. Vectors preferably containing sequences derived from bacterial vectors are taught at column 5, lines 15-16. A vector

construct lacking the enhancer cassette and marker are taught at column 9, lines 2-4. Human immunoglobulin κ locus is taught at column 3, line 52. The '449 patent does not teach vectors encoding all of the C domains of a secretory antibody.

The '846 patent teaches construction of an idiotype/GM-CSF fusion protein using murine B-cell tumor 38C13 cells and Vh and Vl genes of the 38C12 tumor cells ligated to human Igγ and Igκ constant region genes in the heavy and light-chain expression vectors pSV2-ΔHGPT and pSV184-ΔHneo (column 4, lines 50-67 to column 5, lines 1-24). Construction of the vectors is shown in detail in Figures 1A and 1B.

The '150 patent teaches vectors for expression of recombinant antibody-cytokine fusion proteins produced in malignant B cells, including GM-CSF-Ig fusion proteins (abstract). Nucleic acid constructs are taught at column 5, lines 54-67 to column 6, lines 1-60. Chimeric immunoglobulins, including sequences comprising DNA of mouse origin and human origin are taught at column 2, lines 55-67. Mouse κ light chain 3' UTR sequences are taught at column 3, line 51. All three C-domains of a secretory (IgG) immunoglobulin (CH1, CH2, and CH3) are taught at Figure 2A. Hybridomas are taught at column 6, line 43. Plasmid construction is taught at column 7, lines 7-48. Ig-GM-CSF conjugate vectors are taught at column 10, lines 5-26.

It would have been prima facie obvious for one of ordinary skill in the art to combine the teachings of the '449, the '846, and the '150 patents because the addition of more than one constant domain of a secretory immunoglobulin (IgG CH1, CH2, and CH3) provide more cleavage sites so that the cytokine may be cleaved from any part of the heavy chain once it reaches its desired target (see '150 patent, column 2, lines 55-62). It is recognized that having multiple heavy chains would increase the likelihood of being recognized by more than one regional protease that would cleave within or proximal to the sequence. Additionally, the '150 and '846 patents both teach the use of chimeric antibodies having both human and murine domains. Chimeric antibodies would have been preferable to purely murine antibodies because they would be slightly less antigenic to the host immune system, thus increasing the ability of the fusion protein to find its target. One reasonably would have expected success because the successful construction of Ig-cytokine vectors, including Ig-GM-CSF to produce biologically useful fusion proteins is old well known in the art.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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